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WHEN A RAT RUNS COLD AND HOT...

Freeze Lesion-induced Focal Cortical Dysplasia Predisposes to Atypical Hyperthermic Seizures in the Immature Rat

Scantlebury MH, Ouellet PL, Psarropoulou C, Carmant L

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PURPOSE: To determine the effects of focal cortical dysplasia on the behavioral and electrographic features of hyperthermia-induced seizures (HSs) in rats.

METHODS: A right sensorimotor cortex freeze lesion was induced in postnatal day 1 (P1) rat pups, and HSs were provoked at P10 under continuous monitoring of core temperature; EEGs were recorded from the right amygdala during and after hyperthermia. Controls included both sham-operated at P1 and naïve rats.

RESULTS: HSs began with jaw myoclonus, followed by hindlimb clonus and generalized convulsions (GCs), and terminated by a period of posthyperthermia depression. The threshold temperature and latency of jaw myoclonus were similar across the groups. However, both the threshold temperature and latency of GCs were significantly lower in lesioned pups than in controls ($40.5 \pm 0.5^\circ\text{C}$, n

$= 24$, vs. $42.0 \pm 0.2^\circ\text{C}$, $n = 21$; $P < 0.001$; 6.7 ± 0.6 min, $n = 20$, vs. 8.4 ± 0.6 min, $n = 22$; $P < 0.05$). In lesioned pups, the threshold and latencies for jaw myoclonus and hindlimb clonus were similar, whereas in controls, the progression from one to the other was marked by significant differences in both parameters. Posthyperthermia depression was longer in lesioned (13.3 ± 1.2 min, $n = 21$) than in control (8.0 ± 0.8 min, $n = 20$; $P < 0.0001$) pups. Ictal EEG activity was recorded during both behavioral seizures and posthyperthermia depression.

CONCLUSIONS: An HS in rats with a localized freeze lesion results in lower threshold GC and prolonged ictal manifestations, thus supporting a pathophysiologic link between focal cortical dysplasia and atypical febrile seizures, conditions that have a high prevalence in children with mesial temporal lobe epilepsy.

COMMENTARY

Tremendous advances in our understanding of the mechanisms and consequences of febrile seizures (FSs) have been made over the past 5 years (1). For example, clinical research using magnetic resonance imaging (MRI) has demonstrated structural lesions after prolonged FSs in some individuals, but not in others (2). Genetic approaches have pinpointed at least eight genes that may predispose to the occurrence of FSs and, perhaps, to the evolution of epilepsy in individuals who have sustained FSs (3). However, human research has been hampered by the difficulty of distinguishing the potential contribution of the FSs per se to these structural lesions or to the epileptogenesis, from potential effects of other genetic or acquired predisposing factors. For example, the sodium- and other ion-channel mutations in families with GEFS+ promote FSs alone in some affected individuals, FSs and generalized epilepsy in other family members, and phenotypically diverse epilepsy alone in yet others (3). Thus the specific contribution of these mutations, of fever, of febrile or other types of seizures, of other gene changes [e.g., cytokine overexpression because of mutation in the interleukin gene (4)], and of structural or functional anomalies of the developing CNS to the occurrence of FSs and their consequences is complex and difficult to sort out in human studies.

However, it may be possible to unravel the roles played by these various influences in controlled experiments with animal models.

Several animal models of FSs have been created and refined (1). The hyperthermic seizures model in rat (5–7) has been popular because of its recreation of key features of human FSs (e.g., fever-like temperatures, low morbidity and mortality) and the facility of its use. This model, adapted to the mouse (8), is suitable for investigating mechanisms of FSs (8) and their consequences for the *normal* CNS (i.e., the CNS free of evident structural or functional alterations that render it susceptible to epilepsy) (5–7).

A second set of FS models is used to define the interactions of these seizures with preexisting vulnerabilities of the developing CNS. These models pursue the two-hit hypothesis that states that the consequences of a given CNS insult will be influenced by the preexistence of otherwise silent vulnerability (9). Such models for FSs include prenatal methylazoxymethanol acetate (MAM) administration to generate disordered neuronal migration (10) and the model discussed here by Scantlebury et al. The authors recreated focal cortical dysplasia in the rat, by using freeze lesions that were performed on the first postnatal day. They then queried whether the lesions generate increased vulnerability to experimental FSs.

The results can be summarized as follows:

1. As found by others (5–7), both the behavioral and the EEG onset of the hyperthermia-evoked seizures commenced within the limbic circuit and then generalized.
2. A neocortical lesion did not alter the threshold temperature to the onset of the initial limbic phase of the hyperthermic seizures. These seizures were characterized by behavioral arrest and jaw myoclonus, that is, chewing and licking motions (5,6). The latency to seizure onset was actually longer in the lesioned pups (perhaps attributable to their lower baseline core temperature; see subsequent discussion).
3. The neocortical lesion, perhaps together with other sequelae of the neonatal procedure, promoted rapid generalization of the experimental FSs, as measured by diminished additional temperature elevation required for evoking generalized seizures. Thus, whereas threshold temperatures for the onset of *limbic and focal motor* (clonic) seizures did not distinguish between lesioned and control groups, threshold to *generalized* seizures was lower in lesioned rats.

The article by Scantlebury and colleagues presents an interesting approach to studying the interaction between preexisting lesions and early life seizures and to analyzing the effects of such interaction on seizure outcome. However, common to analogous models, the approach raises several conceptual points. First, the original intervention or first hit (exemplified here by the freezing lesions) also changes other characteristics of the CNS that are difficult to control and that might be potential confounders in future studies. For example, the survivors of the procedure (the authors report a 10% mortality) have lower core temperature, typical of less well-developed rats, leading the authors to speculate that there may have been retardation of brain growth and maturation. It would be helpful to know brain weights of the lesioned rats as well as measures of synaptogenesis and neurogenesis. The latter, in particular, is expected to be influenced by the substantial stress of the neonatal surgical procedure, and reduced neurogenesis might influence seizure outcome (11). Second, the first hit also may change the parameters of the second hit (i.e., the hyperthermia-evoked seizures). The authors reported increased duration and enhanced severity of the hyperthermic seizures in lesioned pups. This fact might hamper studies that aim to distinguish whether the effects of the second hit (FSs) are more deleterious in lesioned pups, because this comparison will not involve seizures of similar severity. Therefore in studying potential sequelae of these seizures, it will be helpful to include controls who lack the “first hit” but who sustain a “second hit” of the same magnitude as that of lesioned rats.

In summary, the report by Scantlebury et al. contributes to the experimental armamentarium available for the study of the mechanisms and consequences of FS. This model provides an experimental system for elucidating the molecular mechanisms triggered by early-life cortical lesions that influence FSs. Determining the specificity of the cortical lesion and discerning its effects from those of generalized stress responses evoked by the surgical intervention will further increase the value of this model for understanding human FSs and their consequences.

by Tallie Z. Baram, M.D., Ph.D.

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